(4)

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/018,761	06/10/2002	David J Glass	REG 720-US	4464

7590 09/23/2004

Laura Fischer
Regeneron Pharmaceuticals Inc
777 Old Saw Mill River Road
Tarrytown, NY 10591

EXAMINER	
ALONZO, NORMA LYN	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 09/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/018,761	GLASS ET AL.	
	Examiner	Art Unit	
	Norma C Alonzo	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41* is/are pending in the application.

4a) Of the above claim(s) *3-5,7-33,36-38,40-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,6,34,35 and 39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/21/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election without traverse of Group 1, claims 1-2, 6, 34-35, and 39 in the reply filed on 8/19/04 is acknowledged. Whereas Applicant's election of Group 1 does not encompass claims requiring a species election as cited in the office action of 7/26/04 wherein claims requiring a species election have been withdrawn, an election of species is deemed not necessary.

2. Claims 3-5, 7-33, 36-38, and 40-41 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected elections, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 8/19/04.

3. Claims 1-2, 6, 34-35, and 39 have been amended.

4. Claims 1-2, 6, 34-35, and 39, drawn to a method of inhibiting atrophy in skeletal muscles comprising treatment of cells with an inhibitor of Ras, are pending and are under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-2, 6, 34-35, and 39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400 , 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised

and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The breadth of the claims encompasses an *in vitro* or *in vivo* method of inhibiting atrophy or causing muscle hypertrophy in mammalian skeletal muscle cells comprising treating the cells with an inhibitor of the Ras/Raf/Mek/Erk pathway wherein the inhibitor inhibits Ras wherein the inhibitor is PD98059 or farnesyl transferase.

Wherein the nature of the invention is a method of inhibiting atrophy or causing muscle hypertrophy comprising inhibiting the Ras/Raf/Mek/Erk pathway and more specifically, Ras, it is well known in the art at the time of the invention that Ras interacts with several effector proteins such as "Raf kinases, phosphatidylinositol 3-kinase (IP-3), RalGEFnad NORE/MSTI." However, while the basic mechanics of Ras signaling have been research extensively, varying effects have still been seen in Ras studies thought to be variable mediation of effects by Ras isoforms. Hancock, J.F. (Nat Rev Mol Cell Bio 4:373-384, 2003) teaches that these isoforms have also been shown to have variable biological effects. For example, "H-ras andK-ras activate Raf-1 and Pi3K with varying efficiencies: K-ras is the more potent activator of Raf-1, an H-ras the more potent activator of PI3K." The author teaches that, "biochemical differences between Ras isoforms translate into biological differences." An example the authors cites is that "biological assays of Ras function, including cell growth, transformation and survival, also show differences between isoforms." For example, McGlynn et al. (Leuk Res 24:47-54, 2000) teach that while Ras and Raf extended the exponential growth phase of

FDC-p1 cells under conditions of optimal growth, under conditions of factor withdrawal, only oncogenic Ras was able to significantly promote survival of FDC-P1 cells. Activated Raf was unable to afford a significant reduction in factor dependence in all of the conditions tested. (page 52, paragraph 1) The authors suggest that "alternative downstream targets of Ras may be promoting the survival of these cells. Such targets include PI3K, shown previously to promote cell survival through AKT." (page 52, paragraph 2)The authors conclude that, "while signaling pathways involving Raf are important in mediating the pro-proliferative effects of mutant Ras in haematopoietic cells, alternative mediators are important in promoting the anti-apoptotic effects of this oncogene." (page 53, paragraph 4) Further, the state of the art shows that Ras activation and not Ras inhibition is a mechanism by which to induce hypertrophy of cardiac myocytes. For example, Hunter et al. (J Biol Chem 270(39): 23173-23178) teach a transgenic mouse having cells expressing oncogenic ras in the cardiac ventricular chamber (pae 23174, paragraphs 1-2). The authors teach generation of said mice comprising microinjecting into mouse oocytes a oncogenic human Ha-ras cDNA subcloned into a eukaryotic expression vector containing the MLC-2V promoter. (page 23174, paragraph 6) Wherein the authors monitored the presence of a hypertrophic phenotype by measuring an increase in chamber mass, an enlargement of myocardial cell size, and the activation of a marker for the embryonic gene program, (page 23175, paragraph 2) the authors teach that "ras is sufficient to activate a hypertrophic response in cardiac muscle in the *in vivo* context." (page 23177, paragraph 2) Gottshall et al. (Proc Natl Acad Sci 94:4710-4715, 1997) also teach ras transgenic mice with an

enhanced ventricular hypertrophic phenotype. Wherein the authors generate (MLC)-Ras transgenic mice, said mice "manifests functional, morphological, and molecular features strikingly similar to human hypertrophic cardiomyopathy." (page 4715, paragraph 3) Further, Thorburn et al (J Biol Chem 268(3): 2244-2249, 1993) teach an *in vitro* model of Ras activation wherein injection of activated Ras induces expression of both the c-fos and atrial natriuretic factor genes. "Expression of both these genes is associated with the hypertrophic response in ventricular myocytes suggesting that Ras is involved in the hypertrophic signaling pathway." (page 2244, paragraph 1) Finally, Proud CG recently taught, "The potential importance of Ras signaling in cardiac hypertrophy is underlined by the observation that transfection or microinjection of cardioimyocytes with an activated Ras mutant (V12Ras) leads to changes in gene expression similar to those seen in hypertrophy. Furthermore, Ras causes myofibrillar changes and other effects characteristic of hypertrophy. Perhaps most significantly, targeted overexpression of V12Ras in mouse heart caused ventricular hypertrophy and cardiac failure." (page 404, paragraph 1) Therefore, because of the presence of variant isoforms of Ras that invoke varying biological effects and studies showing Ras activation, and not inhibition, induces hypertrophy cardiac cells, the state of the art of Ras inhibition in a method of inhibiting atrophy or causing hypertrophy is unpredictable. While the level of skill of an artisan practicing the claimed invention will be high, in view of the unpredictability of the state of the art, an artisan would require specific guidance to carry out the full breadth of the claimed invention.

Wherein the state of the art of inhibition of Ras as a means of inhibiting atrophy or causing hypertrophy in mammalian skeletal muscle cells is unpredictable due to the variable isoforms of Ras and the state of the art of Ras research that shows activation, and not inhibition, of Ras induces hypertrophy, coupled with the inability to extrapolate the biologic effect of Ras inhibition from the biologic effect of Raf inhibition, it would take a skilled artisan specific guidance from the instant specification to make and use the claimed invention.

The working example in the specification describes an *in vitro* and *in vivo* model of inhibition of Raf comprising a mouse model for testing muscle atrophy comprising immobilization of the ankle joint of mice or rats to induce atrophy of the muscles at the ankle joint (pages 18-19, see Example 2) or C2C12 cells transformed with a construct comprising cDNA encoding constitutitvely active or dominant negative Raf gene (pages 19-20, see Example 4). Said *in vitro* working example teaches that "myotubes expressing the dominant negative form of Raf were found to be much larger than control myotubes – the myotubes were longer, and had broader diameters. (page 17, lines13-19) Said working example does not teach a working *in vivo* model for testing atrophy or with or without Ras. Whereas the specification describes the procedure to immobilize the ankle joints of rodents and muscle tissue is removed and weighed, a skilled artisan is not taught a method to treat with a Ras inhibitor or with any type of inhibitor. The working example does not teach a method of administration, dose, or timecourse of treatment by any Ras inhibitor such that muscle atrophy is inhibited or muscle tissue hypertrophy is shown. The working example does not teach the use of PD98059 in

either the *in vivo* model for testing muscle atrophy or the *in vitro* model of muscle atrophy comprising C2C12 cells. Without specific guidance, a skilled artisan would have to determine dose, method of administration, and method of assaying efficacy of PD98059 on muscle atrophy. Further, the state of the art does not teach that treatment of mammalian muscle cells with PD98059 inhibits atrophy or causes hypertrophy. For example, Ushio-Fukai et al. (J Bio Chem 273(24): 15022-15029) teach that treatment of cultured vascular smooth muscle cells with PD98059 only partially, but significantly attenuates angiotensin II-induced hypertrophy. (page 15026, paragraph 5) Without specific guidance to use PD98059, it would be an undue burden of experimentation on a skilled artisan to make and/or use an *in vivo* or *in vitro* method to inhibit atrophy or induce hypertrophy of muscle cells with PD98059. Further, wherein the claims are drawn to a method using farnesyl transferase, the disclosure does not teach treatment of mammalian muscle cells with farnesyl transferase such that atrophy of said cells is inhibited or that hypertrophy of said cells is induced. Whereas the state of the art of farnesyl transferase does teach that treatment of vascular smooth muscle cells of the cardiovascular system with farnesyl transferase inhibitors inhibits hypertrophy. For example, Works et al. teach that porcine vascular smooth muscle cells treated with FPTIII, a farnesyl transferase inhibitor, for 18 to 24 hours "inhibited platelet-derived growth factor (PDGF) -induced [^{3}H] thymidine incorporation into DNA, providing direct evidence that FPTIII inhibits cell proliferation." (page 1540, paragraph 2). The state of the art, however, does not teach treatment of said cells with farnesyl transferase such that atrophy was inhibited or hypertrophy was induced in said cells. Therefore, in view

of the unpredictability of the biological effect of farnesyl transferase in light of its effect on Ras and the unpredictability of the art of Ras as discussed above and the lack of specific guidance to use farnesyl transferase in mammalian skeletal muscle cells to inhibit atrophy or induce hypertrophy, it would take an undue burden of examination for a skilled artisan to determine if treatment of cardiac smooth muscle cells with farnesyl transferase would inhibit atrophy or cause hypertrophy. Finally, whereas the rest of the disclosure only generally discusses methods for identification of agents, genes, and gene products that interfere with the Ras/Raf/Mek/Erk pathway as a means to inhibit skeletal muscle atrophy such as contacting said agent with muscle cells expressing constitutively active mutant forms of Ras or using said agents in mammals having an atrophic condition, there is no specific guidance as to how a skilled artisan would inhibit Ras in an *in vitro* or *in vivo* method to inhibit muscle cell atrophy or cause hypertrophy in a mammal. Therefore, in view of the lack of specific guidance provided by the specification to modify models of the effect of Raf inhibition on muscle atrophy by Ras inhibition, the lack of specific guidance to use a working *in vivo* model of testing for muscle hypertrophy, the unpredictability of the art and lack of specific guidance by the disclosure to use any Ras inhibitor, PD98059, or farnesyl transferase in mammalian skeletal muscle cells to inhibit atrophy or induce hypertrophy, it would take an undue burden of experimentation for a skilled artisan to make and use the two methods of inhibiting atrophy or causing hypertrophy in mammalian skeletal muscle cells of the claimed invention.

Therefore, in view of the the lack of guidance provided by the specification as to how to modify a Raf-directed method to inhibit muscle atrophy or cause muscle hypertrophy using Ras inhibitors and the lack of specific guidance to use an *in vivo* method to test muscle atrophy, as well as the unpredictability of the art of Ras inhibition on muscle atrophy or hypertrophy, one of ordinary skill in the art at the time of the invention would have required extensive experimentation to determine which Ras inhibitors to use, what dosage and what route of administration to use to inhibit atrophy or cause hypertrophy in mammalian skeletal muscle cells. It would therefore represent an undue burden of experimentation on an artisan to make and use the claimed invention, a method of inhibiting atrophy or causing muscle hypertrophy in mammalian skeletal muscle cells comprising treating the cells with an inhibitor of the Ras/Raf/Mek/Erk pathway wherein the inhibitor inhibits Ras wherein the inhibitor is PD98059 or farnesyl transferase.

7. Claims 1, 2, 34, and 35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The invention of Claim(s) 1, 2, 34, and 35 encompasses a method of causing atrophy or muscle hypertrophy in mammalian skeletal muscle comprising treating the cells with any inhibitor of the Ras/Raf/Mek/Erk pathway.

The inhibitor of these claim(s) are broad in scope, being defined on the basis of their effect, and not on any specific structure. The specification broadly discloses these inhibitors as "those already proven to be pharmacological antagonists for Ras." (page 5, lines 11-12)

In analyzing whether the written description requirement is met for gene claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, the specification describes only the effect of PD98059 on Phas-1 expression, a molecule involved in protein synthesis (page 17, line 27 - page 18, line 4). The instant specification does not discuss the chemical and physical structure of farnesyl transferase. The instant specification does not discuss the chemical and physical structure of any other inhibitor of Ras in the pathway other than PD98059. The specification does not provide any disclosure as to what would have been the required structure which would allow one to distinguish the various species of the genera. Next then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e., other than nucleotide sequence), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, the only other characteristics that could differentiate one inhibitor from another would be efficacy in inhibiting atrophy or causing hypertrophy in C2C12 cells or ankle joint tissue of mice or

rats or chemical composition of the individual agents. However, all the inhibitors may have such functional property and therefore this characteristic cannot be used to distinguish other members of the genus. Therefore no function, physical structure, or chemical composition is given for the broad genus of "inhibitors" that could distinguish the members of the genus such that the disclosure does not allow one of skill in the art to distinguish the different members of the genera from each other.

Applicant's attention is directed to *In re Shokal*, 113 USPQ 283 (CCPA 1957), wherein it is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. *In re Soll*, 25 CCPA (Patents) 1309, 97 F2d 623, 38 USPQ 189; *In re Wahlforss*, 28 CCPA (Patents) 867, 117 F2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

In conclusion, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of any inhibitor of Ras, at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1 and 34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are directed to a method comprising "treating cells." This term does not constitute an active step of a methods claim.

9. Claims 1 and 34 are rejected under 35 U.S.C. 112, second paragraph, as being drawn to non-elected subject matter. Applicants have elected Ras, as set forth in the office action of 8/19/04. The subject matter Raf, Mek, and Erk are therefore non-elected subject matter. Correction of claims is required.

10. Claims 6 and 36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite. The claim is directed to an inhibitor of the Ras/Ref/Mek/Erk pathway wherein the inhibitor is PD98059 or farnesyl transferase. Farnesyl transferase is an enzyme that activates the Ras/Ref/Mek/Erk pathway, not an inhibitor of the pathway. It is not clear as to how an activator of Ras could inhibit it? Correction of claims is required.

Conclusion

11. No claims are allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Norma C Alonzo whose telephone number is 571-272-2910. The examiner can normally be reached on 8-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on 571-272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

NCA

RAM R. SHUKLA, PH.D.
PRIMARY EXAMINER